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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/602,833	06/23/2000	Alex Turner	8535-036-999	9468

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EXAMINER	
LI, QIAN J	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/04/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/602,833	TURNER ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 September 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6,8 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 June 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4,15* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment and response filed on 9/5/02 has been entered as paper #16. Claims 1, 3-5 have been amended. Currently, claims 1-6, 8, and 21 are pending and under examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 3-6, and 21 are newly rejected under 35 U.S.C. 102(a) as being anticipated by *NCI-CGAP* (EST database).

Claims 1, 3-6 are drawn to an isolated nucleic acid molecule comprising at least 50 contiguous bases of SEQ ID Nos: 1 or 3, complement thereof; or an isolated nucleic acid molecule that hybridizes under stringent condition to SEQ ID Nos: 1 or 3; an expression vector comprising the nucleic molecule and a host cell comprising the vector.

The reference discloses a nucleic acid molecule having accession number AI399758 in the EST database, which contain 64 contiguous bases of SEQ ID Nos: 1 or

3, respectively, and which share 100% best local similarity with the recited sequences, thus, could hybridize with said sequences. Because the cloning and sequencing process use vectors and host cells containing the nucleic acid, therefore, *NCI-CGAP* anticipates the instant claims.

Claim Rejections - 35 USC § 101 & 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 8, and 21 stand rejected under 35 U.S.C. § 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

Applicants argue that the utilities of the novel protein is provided in the specification, that support for the specific utility is based on the presence in the claimed nucleic acid molecule of the LRR domain that is present in many proteins in the ras signal-transduction pathway, that LRR has been shown to interact with Ras both in vitro and in vivo in yeast; that the newly submitted exhibit D shows that SGT4 shares 34% amino acid sequence identity and 52% amino acid sequence conservation with the LRR domain of human RSU-1, and 34% amino acid sequence identity and 30% amino acid sequence conservation with the LRR domain of human FLI-1, that this high percentage

homology among various LRR-containing genes are comparable to the alignment of the LRR domains of FLI- and RSU-1, and again use the activity of FLI-1 as the support for the asserted utility of SGT4. Applicants further listed other publications in the art disclosing Fli-l sequences of other species sharing 20-30% sequence identity with SGT4 and containing LRR. Applicants argue that the specific and credible utility of SGT4 based on the utility of LRR-containing proteins, and the Examination Guidelines for the Utility Requirement states if the applicant has asserted that the claimed invention is useful for any particular practical purpose and the assertion would be considered credible by a person of ordinary skill in the art, the Examiner should not impose a rejection based on lack of utility.

The arguments have been carefully considered but found not persuasive for reasons of record advanced in Paper #12 and following.

The Examination Guidelines for the Utility Requirement states, "CREDIBILITY IS ASSESSED FROM THE PERSPECTIVE OF ONE OF ORDINARY SKILL IN THE ART IN VIEW OF THE DISCLOSURE AND ANY OTHER EVIDENCE OF RECORD THAT IS PROBATIVE OF THE APPLICANT'S ASSERTION". In the specification and the newly submitted evidence, the asserted utility of the claimed molecule is based on the sequence homology with LRR-containing proteins, and the utility of FLI-1 and RSU-1. Therefore, the critical issue is whether such sequence homology could place the SGT4 in the family of LRR-containing protein family, and whether the specific utility of SGT4 could be supported by the utility of FLI-1 and RSU-1.

In view of the state of the art in protein biology, it is highly unpredictable, based on sequence homology alone, that sequence homologues will have the same activity as that protein to which they are being compared. This is because one cannot accurately predict the effects of the dissimilarities in the sequences identified by SEQ ID Nos: 1 and 3, and of putatively related family members upon protein structure and function. *Bowie et al* (Science 1990 Mar; 247:1306-10) teach that an amino acid sequence encodes a message that determines the shape and function of a protein; and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome. They also teach that the prediction of protein structure from sequence data, and in turn, utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (page 1306, column 1); that while it is known that many amino acid substitutions are possible in any given position, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or none at all (page 1306, column 2). A 30-50% similarity to the LRR domain of FLI-1 would not be considered as high in homology since even one amino acid change in a critical position could cause the change in peptide function, thus, the skilled artisan could not predictably place SGT4 in the family of Ras signal transduction proteins. *Rudinger* (Peptide Hormones 1976; June; pages 1-7) teaches the relationship of sequence components and the peptide hormone function

"THE SIGNIFICANCE OF PARTICULAR AMINO ACIDS AND SEQUENCES FOR DIFFERENT ASPECTS OF BIOLOGICAL ACTIVITY CANNOT BE PREDICTED *A PRIORI* BUT MUST BE DETERMINED FROM CASE TO CASE BY PAINSTAKING EXPERIMENTAL STUDY." (last paragraph of text on page 6). *Everett et al* (Nat Genetics 1997;17:411-22) use sophisticated computational modeling based on sequence homology to determine that the gene product causing Pendred syndrome was a sulphate transporter. However, subsequent research and investigation into the actual functional properties of the protein revealed that the protein was actually a chloride-iodide transporter and not a sulphate transporter as was originally predicted based on sequence homology (*Scott et al,* Nat Genetics 1999 Apr;21:440-443). *Bork* (Genome Res 2000:10;398-400) teaches the power and pitfalls associated with comparative sequence analysis for predicting protein function, and that interacting proteins in one organism sometimes have homologs in other organisms. However, *Bork* pointed out that *Marotte et al* predicted novel interactions for 50% of yeast proteins using tools of gene fusion information, but noted an overlap with classical prediction methods with an error rate of 82% (left column in page 400). Therefore, according to the current levels of the skill, determination of the effects of particular sequence changes is not predictable until they are actually made and used, hence resulting in a trial and error situation. Therefore, the general knowledge and levels of skill in the art do not supplement the omitted description, because specific, not general guidance is what is needed. Therefore, the 30-50% sequence homology alone is insufficient to place SGT4 in Ras signal transduction family, and/or to predict the function of SGT4 in the pathway. Thus, sequence homology alone is insufficient to provide a credible utility for SGT4.

Applicants further argue that Fong reference teaches the identification of two related genes that encode proteins interact with LRR domain of human FLI-1 on the basis of sequence similarities, FLI-1 belongs to a subclass that binds to GTPase-like signaling molecules, thus, the teaching supports the instant claimed invention base on the sequence homology among the LRR domains of various proteins.

The argument has been fully considered but they are not persuasive. This is because 1) In Fong reference, the sequence analysis is not solely based on the overall sequence homology, but through comparison of a critical region of the conserved coiled-coil domain, which showed a homology from 68% to 97%, and a sequence similarity from 84%-99% for LRRFIP1 and LRRFIP2 (page 153, left column). From the functional perspective, the folding structural similarity is much more reliable than overall sequence homology. 2) even though Fong et al concluded that the FLI belongs to a family of proteins in Ras signaling pathway, the precise biological function of the FLI proteins have not determined, this has been made clear in the abstract. Thus, it is unacceptable to use FLI protein as support for the novel protein of instant invention, which shares only 30-50% similarity with FLI at the critical LRR domain, wherein the function of FLI proteins in signaling of Ras transduction have not yet been determined.

With regard to the asserted utility stated in the specification for use as probes and primers for detecting SGT4 genes or LRRs-containing gene, for chromosome mapping, in Southern and Northern analyses, and in situ hybridization assays, the issues have been addressed in Office action Paper #12, pages 6-8, and only part of the last paragraph on page 8 will be reiterated as following, "the sole *immediate* utility

constitutes research on the claimed product itself (which is a non-statutory utility) in order to determine a specific and substantial statutory utility for the claimed invention. Practice of these disclosed utilities would first require further research on the disclosed sequences itself, i.e. there is no apparent immediate benefit to the public. *Brenner v. Manson*, 148 USPQ 689, 696 (US SupCt., 1966), noted that "CONGRESS INTENDED THAT NO PATENT BE GRANTED ON A CHEMICAL COMPOUND WHOSE SOLE 'UTILITY' CONSISTS OF ITS POTENTIAL ROLE AS AN OBJECT OF USE-TESTING", and stated, in the context of the utility requirement, that "A PATENT IS NOT A HUNTING LICENSE. IT IS NOT A REWARD FOR THE SEARCH, BUT COMPENSATION FOR ITS SUCCESSFUL CONCLUSION."

Because the claimed invention is not supported by a specific and substantially asserted utility or a well-established utility for the reasons of record and set forth above, the specification fails to meet the utility requirement for claimed invention.

Claims 1-6, 8, and 21 are rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by a well established utility for the reasons set forth in the rejection under § 101 above, one skilled in the art would not know how to use the claimed invention.

Applicants argue that the specification teaches and it is routine in the art to make the polynucleotides containing or hybridizing to SEQ ID Nos: 1 and 3; and the specific use of such polynucleotide is also taught as indicated in the argument under utility section.

The argument has been fully considered but they are not persuasive because the specification only provides guidance for the use of the recited polynucleotides for further experimentation in the elaboration of potential proteins encoded by the claimed polynucleotides are functional in Ras signal transduction pathway; or for the use of the claimed nucleic acids in, for example, chromosome mapping, tissue-type identification, or treating and diagnosing a disease. The first use represents an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed nucleic acids. The second use represents a function that is manifest in the polynucleotide itself and does not require, *a priori*, that the nucleic acid encode any particular product *per se*. The specification fails to teach a particular chromosomal location that could be used for mapping, a particular tissue that is exclusive for SGT4 expression, or a particular disease that could be diagnosed by SGT4 probe, or a particular function in the Ras signaling pathway that could be regulated by SGT4, therefore, fails to teach how to use the claimed invention.

Accordingly, for reasons of record and those of foregoing, the specification fails to meet the statutory enablement requirement under 35 USC § 112, 1st paragraph.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-

1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
November 27, 2002

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER